.on230

IIIE0300569

WO 2004/004571

PCT/IL2003/000569

ART 34 AMDT

63 -

<u>Claims</u>

- 1. A method for neutralizing accustically active particles immersed in a flowing fluid, in which:
 - (a) ultrasonic waves are provided, which propagate through said fluid, said ultrasonic waves pushing said particles in the direction of a friction layer near a surface or surfaces in contact with said fluid or pushing said particles against the direction of flow of said fluid, thereby causing the motion of said particles to stop; said ultrasonic waves additionally causing said particles to be held in place by pushing them against said surface or surfaces or against the flow of said flowing fluid; and
 - (b) an acoustic radiation force is provided for neutralizing said ultrasonically active particles which have been stopped and held in place;

characterized in that, said acoustically active particles are neutralized within the flowing fluid by one or a combination of the following processes:

i. a deformation process; wherein an acoustic field is provided which is modulated at a frequency corresponding to a deformation frequency of said acoustically active particles, thereby surrounding said particles with an asymmetric acoustic radiation force and causing fragmentation of said particles into smaller ones; and

|네일(230 . nu4

ART 34 AMDT

WO 2004/004571

64 -

- ii. a diffusion process; wherein a pulsating acoustic radiation field is provided which alternately compresses and releases said particles, thereby increasing the efficiency of the diffusion of material from the interior of said particle to the surrounding fluid.
- 2. A method according to claim 1, wherein the acoustic radiation force for pushing and the acoustic radiation force for neutralizing are provided by the same source.
- A method according to claim 1, wherein the acoustic radiation force for pushing and the acoustic radiation force for neutralizing are provided by different sources.
- 4. A method according to claim 1, wherein the acoustic radiation force for pushing and the acoustic radiation force for neutralizing are applied as a superimposition of acoustic radiation forces having two or more frequencies and or waveforms.
- 5. A method according to claim 1, wherein the acoustic radiation force for pushing and the acoustic radiation force for neutralizing have waveforms chosen from the group comprising, but not limited to:
 - (a) continuous; and
 - (b) pulsating.

Best Available Copy

AMENDED SHEET 578 P.004

28-09-2004

WO 2004/004571

PCT/IL2003/000569

ART 34 AMDT

65 -

- 6. A method according to claim 1, wherein the acoustic radiation force for pushing and the acoustic radiation force for neutralizing are aimed towards the surface of a wall of the vessel containing the fluid or a surface placed in their path.
- A method according to claim 1, wherein the acoustic radiation force for pushing and the acoustic radiation force for neutralizing are aimed in a direction opposite to the direction of flow of the fluid and along the axis of the vessel through which said fluid flows.
- 8. A method according to claim 1, wherein the acoustic radiation force for pushing and the acoustic radiation force for neutralizing are focused,
- 9. A method according to claim 1, wherein the acoustic radiation force for pushing and/or the acoustic radiation force for neutralizing are generated upon detection of the acoustically active particles by a detector or detectors.
- 10.A method according to claim 9, wherein the detector is chosen from the group comprising, but not limited to:

DESao.

WO 2004/004571

PCT/IL2003/000569

ART 34 AMDT

66 -

- (a) an ultrasonic detector; and
- (b) an electro-optic detector.
- 11.A method according to claim 9, wherein the detection is made by detecting ultrasonic energy sourced emitted by an ultrasonic transducer, refracted by the particles, and detected by said transducer.
- 12.A method according to claim 9, wherein the detection is made by detecting ultrasonic energy emitted by an ultrasonic transducer, refracted by the particles, and detected by a different transducer.
- 13.A method according to claim 1, wherein the flow of the fluid is through a vessel that is open to view.
- 14.A method according to claim 1, wherein the flow of the fluid is through a vessel that is surrounded by an object and therefore is not open to view.
- 15.A method according to claim 14, wherein the orientation of the vessel is determined with the aid of ultrasonic detectors which detect the flow of fluid through said vessel.

II_IL0300569

. 00230

רַנים.

WO 2004/004571

PCT/IL2003/000569

ART 34 AMDT

. 67 -

- 16.A method according to claim 15, wherein the external object is a human body.
- 17. A method according to claim 16 wherein the vessel is a blood vessel.
- 18.A method according to claim 16 wherein the vessel is the carotid artery.
- 19.A method according to claim 1, wherein the surface is one or a plurality of membranes and large acoustically active particles break apart into smaller particles, which pass through the openings in said membranes upon impact.
- 20.A method according to claim 19, wherein the size of the pores in the membranes is between 0.1 μ m to 1mm.
- 21.A method according to claim 19 wherein the membranes together with the ultrasonic propagating field acting on the acoustically active particles effectively act as a semi-permeable membrane which permits particles to leave the fluid flow through the pores of said membranes and prevents the particles from reentering the flow by means of: the ultrasonic force alone, as a result of the

WO 2004/004571 PCT/IL2003/000569

ART 34 AMDT

68 -

merger of the smaller bubbles that have passed through the openings in said membrane resulting in a bubble that is larger than said openings, or by a combination of both effects.

- 22.A method according to claim 19, wherein there is an array of open cells on the side of the membrane surface opposite to the flow of the acoustically active particles and wherein after particles are broken apart and pass through the openings of said membrane, they enter said cells thus preventing them from recombining to form particles whose dimensions exceed that of said cells.
- 23. A method according to claim 1, wherein the surface comprises an array of cells arranged in a honeycomb pattern.
- 24. A method according to claim 19, wherein the acoustic pressure exerted on acoustically active particles that are larger than the pore size of the membrane causes them to deform without breaking apart upon impact with said membrane and slip through said pores, regaining their original shape after slipping through said membrane.

8.SEP.2004 15:47

LUZZATTO&LUZZATTO 972 B 6467080

PCT/IL2003/000569

פענוי.

WO 2004/004571

ART 34 AMDT

.on230

69 -

- 25.A method according to claim 19 where the dimensions of the pores of each succeeding membrane in a plurality of membranes become smaller in the direction of the fluid flow.
- 26.A method according to claim 1, wherein the acoustically active particles comprise an encapsulated material.
- 27.A method according to claim 26, wherein the encapsulated material is a drug.
- 28. An ultrasonic system for using the method of claim 1 to neutralize acoustically active particles immersed in a flowing fluid, said apparatus comprising:
 - (a) a fluid flow path through a vessel;
 - (b) a surface which creates a friction layer to the fluid that flows adjacent to it, and can be partially or fully submerged in the fluid, or may consist of a wall of said vessel or a type of membrane;
 - (c) transducing means acoustically connected to said vessel or submerged in it, said transducing means delivering ultrasonic waves that propagate through said fluid, said ultrasonic waves pushing said particles in the direction of said friction layer near a surface or surfaces in contact with said

IIIL0300569

WO 2004/004571

PCT/IL2003/000569

. on230

ART 34 AMDT

70 -

fluid or pushing said particles against the direction of flow of said fluid;

wherein said transducing means are additionally capable of delivering one or more of the types of acoustic radiation fields selected from the following group:

- (i) a pulsating acoustic radiation field, which alternately compresses and releases said particles; and
- (ii) an acoustic field which is modulated at a frequency corresponding to a deformation frequency of said acoustically active particles.
- 29. A system according to claim 28, wherein the surface is a layer of the flowing fluid and the acoustic energy is directed opposite to the direction of flow.
- 30. A system according to claim 28, wherein the acoustic energy is focused.
- 31.A system according to claim 29, wherein the fluid flows in a tube.
- 32. A system according to claim 28, wherein the transducing means comprise an ultrasound head comprising one or more ultrasound transducers.

Best Available Copy

28-09-2004

. pn230

WO 2004/004571

PCT/IL2003/000569

ART 34 AMDT

71 -

- 33.A system according to claim 32, wherein the number of ultrasound transducers is at least three and two of said transducers are used to detect the presence of acoustically active particles and to influence the operation of the remainder of said transducers.
- 34. A system according to 32, wherein the transducing means are comprised of a disc shaped main transducer surrounded by an outer ring shaped transducer, said outer transducer being driven in an anti-phase manner to said main transducer.
- 35. A system according to claim 32, wherein the acoustic energy is focused.
- 36.A system according to claim 32, wherein the acoustic energy is unfocused.
- 37. A system according to claim 28, wherein the system comprises means for providing ultrasonic energy for selectively stopping, breaking apart, shrinking, and dissolving acoustically active particles immersed in blood flowing in the carotid arteries.
- 38. A system according to claim 37, further comprising a disposable pillow.

WO 2004/004571

PCT/IL2003/000569

ART 34 AMDT

72 -

- 39.A system according to claim 37, wherein the system comprises two ultrasonic heads one located on each carotid artery.
- 40. A system according to claim 37, comprising two ultrasonic heads each at least two ultrasonic bubble detectors for detect comprising acoustically active particles and/or fluid flow and at least one ultrasonic transducer to provide the ultrasonic energy.
- 41. A system according to claim 28, wherein the surface is a membrane or has a honeycomb structure to aid in breaking apart and/or holding the acoustically active particles.
- 42.A system according to claim 41, wherein the membrane acting together with the acoustic energy effectively acts as a semi-permeable membrane, which acts to remove acoustically active particles from the flowing fluid in which they are immersed.
- 43.A system according to claim 28, wherein the vessel through which the fluid flows is an arterial line of cardiopulmonary machine, contrast media catheter, or dialysis machine or a high-flow venous line.
- 44.A system according to claim 28, wherein the acoustically active particles comprise encapsulated material.

II/L0300569

.on230

PCT/IL2003/000569

WO 2004/004571

. 4..._

ART 34 AMDT

73 -

- 45.A system according to claim 44, wherein the acoustically active particles are delivered to a selected location in a vessel by the flowing fluid, concentrated at said location within said vessel and the encapsulated material is released at said location by shrinking and/or breaking apart and/or dissolving said particles.
- 46.A system according to claim 45, wherein the acoustically active particles are introduced into the flowing fluid using a specially designed balloon catheter.
- 47.A system according to claim 44, wherein the encapsulated material is a drug.
- 48. A system according to claim 45, wherein the vessel is part of the vascular system of a human or animal body.